Dietary Sodium and Potassium-Induced Transient Changes in Blood Pressure and Catecholamine Excretion in the Sprague-Dawley Rat

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SUMMARY When Sprague-Dawley derived rats were changed from a chow type diet to a moderately high sodium diet, rapid transient changes in blood pressure (BP) and catecholamine excretion were observed. After 1 dietary week, BP increased from 122 ± 1 mm Hg to approximately 145 mm Hg (p < 0.001), and there was a concomitant 20% reduction in urinary norepinephrine (UNEV) and epinephrine (UEV) excretion (p < 0.05). Heart rates were reduced (p < 0.05). These data suggest that sodium-induced increases in BP were initially associated with suppressed sympathetic nervous system activity. During dietary Weeks 2 and 3, some animals had a persistent moderate elevation in BP (BP = 150 mm Hg), while others developed more severe increases. UNEV in moderately hypertensive animals returned to control levels during this period; but UEV and heart rates remained suppressed. UNEV in severely hypertensive animals exceeded (13% ± 3%, p < 0.05) that of controls. This increase coincided with their most severe hypertension (171 ± 1 mm Hg, p < 0.001). UE values and heart rate data indicate that systemic adrenergic tone was likely suppressed at this time and that the increased UNEV was renal in origin. By dietary Week 4, the BP of severely hypertensive animals had begun to fall, and indices of sympathetic nervous system tone were indistinguishable among all groups. Inclusion of a dietary potassium supplement ameliorated the development of hypertension only in those animals that became severely hypertensive, and appeared to prevent the early suppression of indices of sympathetic activity. (Hypertension 5: 336-345, 1983)

Key Words • dietary sodium • potassium • hypertension • urinary catecholamines

Clinical, epidemiological, and experimental studies reveal a strong association between dietary sodium content and essential hypertension.1-4 The present consensus appears to be that dietary sodium is causally related to essential hypertension in susceptible individuals. Other studies indicate that dietary potassium may play some modulating role in the hypertensive effects of excess dietary sodium in both animals and in man.5,6,8-14 Meneely et al.8 and later Battarbee et al.15 demonstrated that potassium supplements would lower the elevated blood pressure of the sodium-fed, genetically heterogenous, Sprague-Dawley derived rat. A similar protective effect of potassium was observed in Kyoto spontaneously hypertensive rats (SHR) fed excess sodium,16 Dahl17 salt-sensitive rats (Dahl S), and in the two-kidney, one clip Goldblatt model.18 The mechanisms of both the hypertensive effect of excess dietary sodium and the protective effect of potassium remain unknown.

In the quest for initiating factors or "prime movers" in hypertension,19 exhaustive studies of the relationship between sympathetic neural activity and essential hypertension have been conducted. The topic remains embroiled in controversy. Symbolic of this dispute is a recent review by Goldstein20 who surveyed 32 studies in the area and found 88% of the investigators reporting higher plasma norepinephrine values (PNE) in hypertensives than in normotensives. Only 41% of these differences, however, reached a level considered statistically significant. These higher values were found mostly in young patients, suggesting greater sympa-
thetic nervous system activity may characterize an early stage in the development of essential hypertension that becomes less obvious as hypertension becomes established.

In addition to evidence of enhanced sympathetic nervous system activity, there is also emerging evidence that this increased activity may originate in hormone and sodium-sensitive osmoreceptor areas in the brain. Vascular resistance has been shown to increase after sodium feeding in the Dahl-S rat and in the forearm of humans with borderline hypertension. Intracerebroventricular injections of hypertonic saline lead to pressor responses that are twice as great in the Dahl-S rat as in the Dahl salt-resistant strain (Dahl-R) despite the fact that both strains are fed a low sodium diet. Since greater sympathetic nervous system activity has been shown to be involved in the pressor response to intracerebroventricular injections of hypertonic saline, this suggests a genetically determined central nervous system mediated enhancement of sympathetic responses to a change in cerebrospinal fluid sodium concentration. Interestingly, Goto et al. recently demonstrated that the pressor effects of intracerebroventricular injections of hypertonic saline could be reduced to near that of control animals in the Dahl-S rat by dietary potassium supplements alone, but it was not determined whether sympathetic nervous system activity was "normalized." With respect to sympathetic activity, Battarbee et al. demonstrated that potassium supplements in chronic sodium-loaded rats (1 year) reduced the inappropriately high urinary excretion of norepinephrine and epinephrine along with blood pressure, indicating a potassium-mediated decreased sympathetic activity. Since potassium has been shown to have natriuretic activity, it may influence central pressor responses by enhancing sodium excretion and reducing body sodium content. Decreased exchangeable sodium after potassium loading has been reported, however, revealed no change in intravascular volume in SHR and Wistar-Kyoto rats in response to potassium supplementation while on a high sodium diet. In addition, use of thiazide diuretics, which reduce body sodium content, does not change the response to intracerebroventricular injections of hypertonic saline in the common laboratory rat.

The present study was conducted to examine changes in sympathetic nervous system activity that occur during the formative stages of sodium-induced hypertension and to evaluate any modulating influence that a dietary potassium supplement might have on the process. With the induction of hypertension, hormonal, nervous, functional, and cardiovascular architectural changes soon become so enmeshed that it is impossible to identify the primary dysfunction that led to the elevated pressure. Studies conducted during the formative stages of sodium-induced hypertension, as an animal makes the transition from a low sodium diet and normotension to a high sodium diet and hypertension, should allow better assessment of primary dysfunction.

**Methods**

**Animals and Diets**

Male Sprague-Dawley derived rats were purchased from Holtzman Company and housed one to one in a climate controlled room (23 ± 2°C and 60% ± 10% relative humidity) with 12 hours of light from 6:00 a.m. to 6:00 p.m. Upon arrival, animals were divided into three groups, and after a period of conditioning and observation, placed on special diets consisting of Purina Lab Chow (Bioserve, Inc., Frenchtown, New Jersey) with the following sodium and potassium content: 0.21 mEq Na/g and 0.23 mEq K/g (Control Diet); 0.91 mEq Na/g and 0.24 mEq K/g (High Na Diet); 0.98 mEq Na/g and 0.35 mEq K/g (High Na + K Diet). Deionized water and feed were provided ad libitum. Animal weights and systolic blood pressures (BP) were measured twice weekly over a period of 1 to 4 weeks. Blood pressures and heart rate data were measured using the tail-cuff method and a programmed electrophysgmonomanometer (Narco Biosystems, Houston, Texas). Heart rate was taken from the pulse pressure record of the electrophysgmonomanometer over a period of 30 seconds just before the BP was measured. Animals were introduced to the dietary regimes in a randomized staggered fashion so that the work load on any given day would not be too great.

**Urinary Catecholamines**

Fasting urinary norepinephrine (UNEV) and epinephrine (UEV) levels were determined in a 24-hour urine sample by a modification of the semiautomated trihydroxindole procedure of Viktora et al. The 24-hour urines were collected into 10 ml of 1 N acetic acid which contained 10.0 mg ascorbic acid. After the collection was completed, the sample pH was adjusted to 3.5 to 4.0 with hydrochloric acid, and the samples were frozen at −40°C until analysis. On the day of analysis, the samples were thawed, and 500 mg of disodium ethylenediaminetetraacetate, 50,000 cpm of purified 3H NE, and 10,000 cpm of 14C E, were added to each. Some samples were divided in half and had 0.5 μg of NE and E added to one aliquot of the sample. They were then adjusted to pH 8.2 to 8.5 with sodium hydroxide. All aliquots were immediately chromatographed on 1 × 2 cm acid washed alumina columns. NE and E were eluted from the columns with 0.25 N acetic acid. The samples were then adjusted to pH 6.5 with 0.25 N sodium hydroxide and chromatographed on 0.7 × 4.5 cm weak cation exchange resin columns (Bio-Rex-70) prepared in the sodium form. Norepinephrine and E were the eluted from these columns with 0.25 N acetic acid, and fluorometric analysis was carried out on a Technicon autoanalyzer using a modification of the technique of DeSchaepdryver and Moerman. Recovery of 3H NE was 84.2% ± 1.3% and of 14C E was 69.4% ± 1.3% for the samples analyzed. Recoveries of added "cold" catecholamines, corrected for column losses by using the 3H NE and 14C E recovery, were 103.2% ± 2.3% for NE and 109.2% ± 5.1% for E.

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Statistics

Statistical comparisons were made with the Students’ *t* test, paired *t* test, or analysis of variance (ANOVA) where appropriate. Probability levels of 5% or less were considered significant.

Results

Diet and Blood Pressure

The effects of each diet upon BP over the 4-week dietary periods are depicted in figure 1. Animals with BP > 140 mm Hg were considered hypertensive. Of the 20 animals fed the High Na diet for 4 weeks, only three failed to develop hypertension. All the High Na + K fed animals became hypertensive. Examination of the data at the end of the study suggested that within these Sprague-Dawley rats there were two subgroups over the 4-week course of the study, usually with BP < 150 mm Hg. One subgroup developed more severe hypertension (BP > 150 mm Hg) over the 4-week course of the study, usually with BP near 170 mm Hg. The other subgroup developed only moderate hypertension (BP ≤ 150 mm Hg). These subgroups were selected retrospectively according to their pressure history, and these groups of data were treated separately. At dietary Week 0, before the initiation of the various dietary regimes, the BP of the various groups did not differ significantly, the mean BP ± SEM being 122 ± 1 mm Hg (n = 51) for all groups combined. One week after the initiation of the High Na and High Na + K diets, there was a significant increase in BP when compared to Control-Diet-fed animals. The mean BP was 123 ± 1 (n = 11), 141 ± 2 (n = 10, *p* < 0.001), 145 ± 3 (n = 6, *p* < 0.001), 141 ± 5 (n = 7, *p* < 0.001), and 146 ± 6 mm Hg (n = 10, *p* < 0.001) for the control, High Na BP ≤ 150, High Na BP > 150, High Na + K BP ≤ 150, and High Na + K BP > 150 mm Hg groups respectively. Blood pressures of the moderately hypertensive groups, whether potassium supplemented or not, reached a plateau at approximately 145 mm Hg by the end of the second dietary week where they remained for the duration of the study. Animals that developed more severe hypertension had BP that continued to increase. By the end of dietary Week 2, the High Na BP > 150 mm Hg group had risen slightly but significantly (*p* < 0.025) from Week 1, and that of the High Na + K BP > 150 continued to increase and reached its highest value (162 ± 6 mm Hg, *p* < 0.025). By the end of dietary Week 3, the High Na + K BP > 150 group’s BP began to fall (BP = 157 ± 3 mm Hg), whereas that of the nonsupplemented severely hypertensive group had risen to its highest value of 171 ± 1 mm Hg (*p* < 0.001). The pressure of both severely hypertensive groups continued to decline and by the 4th dietary week they had reached values of 158 ± 5 mm Hg for the High Na group and 149 ± 3 mm Hg for the High Na + K group.

Effect of Diet and Blood Pressure upon Body Weight

Analysis of variance of the body weight and rate of body weight gain for each of the respective dietary periods revealed no significant differences between groups. Since the study was staggered in time, each of the dietary and pressure groups had a broad range of body weights at the end of each dietary week. Body weight data are presented in table 1.

Diet, Blood Pressure, and Heart Rate

Table 2 depicts the effect of the various diets upon the heart rates of animals at the end of each dietary week. There were no significant differences among the various groups at dietary Week 0. After 1 week of dietary sodium loading, heart rates were significantly depressed in all sodium fed groups when compared to their value at Week 0. This depression of heart rate persisted through dietary Week 2 for moderately hypertensive animals and through dietary Week 3 for severely hypertensive animals. The heart rates of potassium supplemented animals were likewise reduced. This suppression was maintained through the third dietary week in the more severely hypertensive animals, whether supplemented or not, but the heart rates of moderately hypertensive animals had returned at this time to levels insignificantly different from that of Week 0. Only the High Na + K BP > 150 group retained this significantly depressed heart rate until the end of the 4th dietary week.
Diet, Blood Pressure, and Catecholamine Excretion Rates: Norepinephrine

The effects of the various dietary regimes upon the 24-hour UNE excretion rate are shown in table 3. No significant differences in the UNEV values among the various treatment groups were found at any time during the 4-week period. There was a tendency for the High Na diet fed animals to have suppressed UNEV when compared to the Control Diet group at the end of dietary Week 1, but ANOVA did not reveal any significant difference ($p < 0.1$).

During the course of the study, it was observed that the excretion rate of NE "tracked" with respect to time, i.e., values for animals that were initially high remained high for the duration of the study, and those that started off low remained low. Figure 2 depicts this tracking phenomenon in representative animals from the Control Diet group. When the data were expressed in absolute terms (µg/kg/24 hr), such variation in basal NE excretion rate within a treatment group made it very difficult to evaluate changes in response to dietary intervention. Even though appreciable changes in NE

### Table 1. Body Weights of Animals Fed Various Sodium and Potassium Diets over a Period of 4 weeks and Grouped According to Blood Pressure

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control diet</td>
<td>11</td>
<td>255 ± 13</td>
<td>301 ± 17</td>
<td>335 ± 16</td>
<td>340 ± 12</td>
<td>356 ± 9</td>
</tr>
<tr>
<td>High Na BP ≤ 150 mm Hg</td>
<td>10</td>
<td>266 ± 20</td>
<td>313 ± 16</td>
<td>338 ± 16</td>
<td>350 ± 17</td>
<td>363 ± 16</td>
</tr>
<tr>
<td>High Na BP &gt; 150 mm Hg</td>
<td>6</td>
<td>241 ± 17</td>
<td>295 ± 18</td>
<td>340 ± 20</td>
<td>359 ± 23</td>
<td>375 ± 26</td>
</tr>
<tr>
<td>High Na + K BP ≤ 150 mm Hg</td>
<td>7</td>
<td>231 ± 26</td>
<td>289 ± 15</td>
<td>316 ± 16</td>
<td>344 ± 14</td>
<td>355 ± 15</td>
</tr>
<tr>
<td>High Na + K BP &gt; 150 mm Hg</td>
<td>10</td>
<td>217 ± 17</td>
<td>317 ± 19</td>
<td>337 ± 18</td>
<td>358 ± 19</td>
<td>362 ± 17</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

### Table 2. Heart Rates of Animals Fed Various Sodium and Potassium Diets over a Period of 4 weeks and Grouped According to Blood Pressures

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control diet</td>
<td>10</td>
<td>404 ± 12</td>
<td>398 ± 9</td>
<td>392 ± 6</td>
<td>383 ± 9</td>
<td>396 ± 6</td>
</tr>
<tr>
<td>High Na BP ≤ 150 mm Hg</td>
<td>9</td>
<td>412 ± 9</td>
<td>384 ± 9†</td>
<td>381 ± 10†</td>
<td>389 ± 10</td>
<td>402 ± 18</td>
</tr>
<tr>
<td>High Na BP &gt; 150 mm Hg</td>
<td>7</td>
<td>446 ± 17</td>
<td>401 ± 10*</td>
<td>396 ± 11†</td>
<td>402 ± 16†</td>
<td>406 ± 17</td>
</tr>
<tr>
<td>High Na + K BP ≤ 150 mm Hg</td>
<td>8</td>
<td>428 ± 8</td>
<td>393 ± 5†</td>
<td>386 ± 7†</td>
<td>392 ± 13</td>
<td>394 ± 17</td>
</tr>
<tr>
<td>High Na + K BP &gt; 150 mm Hg</td>
<td>10</td>
<td>427 ± 9</td>
<td>400 ± 6†</td>
<td>390 ± 7†</td>
<td>397 ± 9†</td>
<td>385 ± 10§</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

* $p < 0.05$ vs Week 0 value.
† $p < 0.025$ vs Week 0 value.
§ $p < 0.005$ vs Week 0 value.

### Table 3. Effects of Sodium and Potassium Feeding on the Urinary Excretion of Norepinephrine over a Period of 4 weeks in Animals Grouped According to their Blood Pressure Responses

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control diet</td>
<td>9</td>
<td>5.1 ± 1.5</td>
<td>5.2 ± 0.6</td>
<td>4.8 ± 0.6</td>
<td>4.4 ± 0.4</td>
<td>4.0 ± 0.4</td>
</tr>
<tr>
<td>High Na BP ≤ 150 mm Hg</td>
<td>10</td>
<td>5.0 ± 0.4</td>
<td>4.2 ± 0.5</td>
<td>5.4 ± 0.6</td>
<td>4.7 ± 0.4</td>
<td>3.9 ± 0.7</td>
</tr>
<tr>
<td>High Na BP &gt; 150 mm Hg</td>
<td>7</td>
<td>4.8 ± 0.5</td>
<td>3.6 ± 0.4</td>
<td>5.5 ± 0.5</td>
<td>5.0 ± 0.5</td>
<td>3.8 ± 0.6</td>
</tr>
<tr>
<td>High Na + K BP ≤ 150 mm Hg</td>
<td>7</td>
<td>4.5 ± 0.4</td>
<td>4.0 ± 0.4</td>
<td>4.5 ± 0.5</td>
<td>5.2 ± 0.6</td>
<td>3.7 ± 0.6</td>
</tr>
<tr>
<td>High Na + K BP &gt; 150 mm Hg</td>
<td>8</td>
<td>5.8 ± 1.0</td>
<td>5.4 ± 0.6</td>
<td>4.9 ± 0.5</td>
<td>6.2 ± 0.8</td>
<td>5.3 ± 0.9</td>
</tr>
</tbody>
</table>

Values are given as means (µg/kg/24 hr) ± SEM.
excretion rate might have occurred for any given treatment group, when all of the group data for a given week were incorporated for statistical analysis, the large differences in basal excretion rates led to great variances within the groups. Figure 2 reveals that within the Control Diet group there were three- to fourfold differences in UNEV between some animals at any given dietary week. To take into account this tracking effect, the basal level of excretion at dietary Week 0 was used to normalize each animal's data for the subsequent dietary weeks, i.e., the UNE data for each animal were expressed as percent of the Week 0 value. Figure 3 illustrates the percent changes in UNE excretion rate for each group and each of the dietary weeks. One week of dietary sodium loading significantly suppressed UNE excretion in the High Na BP ≤ 150 group (-23% ± 7%, p < 0.025) and High Na BP > 150 (-22% ± 11%, p < 0.05) when compared to the Control Diet group value (4% ± 7%). The UNE excretion rate of the high sodium, potassium-supplemented groups was not significantly affected at dietary Week 1, although the High Na + K BP < 150 group approached a near significant suppression (-11% ± 9%, p < 0.1). By the end of dietary Week 2, UNEV of moderately hypertensive groups were comparable to that of the Control Diet group with a trend for the High Na BP > 150 and High Na + K BP > 150 values to be greater. The percentage values were -10% ± 10%, -1% ± 15%, 18% ± 12% (p < 0.1), -5% ± 15%, and 12% ± 23% for the Control, High Na BP ≤ 150, High Na BP > 150, High Na + K BP ≤ 150, High Na + K BP > 150 groups respectively. The tendency of the High Na BP > 150 group UNE excretion rate to be elevated achieved a level considered significantly different (13.3% ± 3%, p < 0.05) from that of the Control Diet group (-18% ± 6%) by the end of the 3rd dietary week. The High Na + K BP > 150 group's UNE excretion rate demonstrated a trend toward an increase (17% ± 16%, p < 0.2) at this time, but the difference was not significant. At the end of dietary Week 4, the values for UNEV were identical for all groups.
Diet, Blood Pressure, and Catecholamine Excretion: Epinephrine

The effect of diet upon the 24-hour UE rate is shown in table 4. As with the data for UNE, there were no significant differences in values among the various groups at any given dietary week when the data were expressed as $\mu g$/kg/24 hr. It was noted that UEV values also tracked with respect to time, like that of the UNEV data (see fig. 4), and when the UEV data were normalized using the initial excretory rate and expressed as percent of initial value, significant differences were obtained. At the end of dietary Week 1, the High Na BP $\leq 150$ and High Na BP $> 150$ group values were significantly lower than that of the Control Diet group ($+20% \pm 19%$), the values being $-21% \pm 7%$ ($p < 0.05$) and $-34% \pm 5%$ ($p < 0.05$) for the two respective groups. There was a tendency for the High Na + K BP $\leq 150$ group to be suppressed, but the variance was too large for a level considered significantly different to be obtained. There were trends toward UEV suppression but no significant differences among the groups for the remaining dietary weeks (fig. 5).

Discussion

It has been demonstrated that the Dahl-S rat, which was derived from the selective inbreeding of the Sprague-Dawley rats, has an exquisite sensitivity to intracerebroventricular injections of hypertonic saline$^{24}$ that leads to increased peripheral adrenergic nervous system activity$^{25-26}$ and an elevated BP. It has been hypothesized that the increased blood pressure in this model may be mediated partly via central nervous system responses to increased dietary sodium intake.$^{27}$ Dietary potassium supplements have been shown to reduce dramatically the pressor response to intracerebroventricular hypertonic saline in the Dahl-S rat$^{27}$ and to prevent the development of hypertension when this strain is sodium loaded. In addition, the classic early

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<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control diet</td>
<td>9</td>
<td>1.4±0.2</td>
<td>1.4±0.2</td>
<td>1.4±0.2</td>
<td>1.4±0.2</td>
<td>1.0±0.1</td>
</tr>
<tr>
<td>High Na BP $\leq 150$ mm Hg</td>
<td>10</td>
<td>1.6±0.3</td>
<td>1.3±0.1</td>
<td>1.5±0.3</td>
<td>1.4±0.2</td>
<td>1.3±0.2</td>
</tr>
<tr>
<td>High Na BP $&gt; 150$ mm Hg</td>
<td>7</td>
<td>1.8±0.4</td>
<td>1.1±0.4</td>
<td>1.7±0.3</td>
<td>1.6±0.3</td>
<td>1.0±0.2</td>
</tr>
<tr>
<td>High Na + K BP $\leq 150$ mm Hg</td>
<td>7</td>
<td>2.2±0.4</td>
<td>1.1±0.2</td>
<td>2.0±0.5</td>
<td>2.0±0.3</td>
<td>1.4±0.2</td>
</tr>
<tr>
<td>High Na + K BP $&gt; 150$ mm Hg</td>
<td>9</td>
<td>1.5±0.4</td>
<td>1.3±0.2</td>
<td>1.4±0.1</td>
<td>1.6±0.3</td>
<td>1.3±0.1</td>
</tr>
</tbody>
</table>

Values are given as means ($\mu g$/kg/24 hr) ± SEM.
work of DeChamplain and coworkers\textsuperscript{36} which showed decreased binding and increased NE turnover rate in selected tissues of DOCA-salt hypertensive rats has been widely interpreted as evidence that peripheral sympathetic nervous system overactivity is the major cause of hypertension in this model. More recently, this concept has been reexamined in the light of studies suggesting an important role for vasopressin\textsuperscript{37,39} and other studies showing that DOCA-salt hypertension can be maintained in peripherally sympathectomized rats.\textsuperscript{40,41}

Recent studies in humans suggest that dietary potassium may exert an important modulating role upon sodium-induced increases in blood pressure in essential hypertensives\textsuperscript{9,12-14} or individuals with a familial predisposition toward essential hypertension.\textsuperscript{10} It has been postulated that, if sodium intake is high, there may occur a relative potassium deficiency in subjects susceptible to the depressor effects of potassium supplements.\textsuperscript{10} This concept is particularly intriguing since dietary sodium excess has been shown to have powerful kaliuretic properties and can lead to a negative potassium balance and a decreased total body potassium.\textsuperscript{32,42} It may well be that the pressor effects of dietary sodium are in part due to potassium depletion in response to sodium loading.

If sodium and/or potassium-induced changes in central nervous system function that lead to enhanced sympathetic nervous system activity are the harbingers of increased blood pressure, then monitoring of indices of sympathoadrenal activity during the transition from a normal sodium diet and normotension to a high sodium diet and hypertension. The effects of a dietary potassium supplement were also studied.

If UEV and UNEV are to be useful indices of systemic sympathoadrenal activity, the renal production of these substances must be taken into account. It has been shown that as much as 25\% of UNEV can derive from renal sympathetic activity per se\textsuperscript{44} and that such activity may exert a significant regulatory influence upon sodium reabsorption without changes in glomerular filtration, renal blood flow, or renal blood distribution.\textsuperscript{45-49} Increased renal sympathetic nervous system activity has been reported to reduce renal sodium excretion by as much as 50\% to 80\%.\textsuperscript{50,54,48} In contrast to these neurally mediated renal effects, circulating levels of NE in the physiological range exert relatively minor effects upon renal sodium and water balance.\textsuperscript{47} Circulating physiological levels of E, however, apparently do have significant indirect effects upon sodium balance.

Since E cannot be produced by the kidney due to the absence of phenylethanolamine-n-methyltransferase and since E is structurally very similar to NE, it is possible to use E excretion as a model of renal catecholamine clearance uncomplicated by intrarenal synthesis. If the plasma NE/E concentration ratio does not change in response to sodium loading, it has been suggested that UEV may be used as an index of general systemic sympathoadrenal activity. The difference between percent E excretion and percent NE excretion would then represent any renal contribution to urinary NE. The data of Boren et al.\textsuperscript{31} demonstrated this effect in a volume-expanded model. A related observation
has been made in dietary sodium-loaded man in which there was suppression of UNEV to a lesser extent than plasma venous levels, presumably due to renal NE production. Studies by Romoff et al. have demonstrated that the plasma NE/E concentration ratio does not change over a broad range of sodium intake in human subjects and renal catecholamine clearance studies of Morganov and Baines indicate that for the Sprague-Dawley rat this is also the case. In addition, the Sprague-Dawley rat's glomerular filtration rate, fractional tubular secretion, and metabolism of catecholamines have been shown to be unaffected by sodium loading in the range of that utilized in this study.

In the present study, we found that Sprague-Dawley derived rats exhibited significant transients in BP and in urinary catecholamine excretion rates over a period of 4 weeks of moderate dietary sodium loading. One week of sodium excess suppressed both UNE and UE excretion rates at a time when BP had risen significantly, inferring that there was an appropriate reduction in systemic sympathoadrenal and renal sympathetic nervous system activity and that some factor other than sodium-enhanced adrenergic activity might be responsible for the early elevation in BP. There was a significant reduction in the heart rates of sodium-loaded animals at the end of the first dietary week, further suggesting decreased sympathoadrenal tone. Volume expansion seemed a likely candidate, but there were no discernable differences in body weight gain among the dietary and BP groups at any time during the study. Body weight variance within each group was large, however, due to the staggered routine used for data collection, and this made it difficult to detect small differences that might have occurred. Vasopressin may be partly responsible for the elevated BP since it has been recently reported to contribute to the maintenance of BP when sympathoadrenal function is impaired.

The inclusion of a small dietary potassium supplement in the high sodium diet had little effect upon the BP increase, suppression of UNE or UE excretion rates, or suppression of heart rates among those animals that developed only moderate hypertension. The inclusion of a potassium supplement in the diet of sodium-fed animals that developed severe hypertension prevented this early UNE and UE excretion rate suppression despite a similarly elevated BP at this time. These data suggest that there was an initial and appropriate suppression of renal and systemic sympathoadrenal tone after acute dietary sodium loading that was associated with an elevated pressure and that an increase in central-nervous-system-generated sympathetic activity was not responsible for the initial increase in BP. Potassium supplementation in animals that later developed more severe hypertension did not result in a great suppression of systemic or renal adrenergic tone at the end of one week.

During the second and third dietary weeks, the UE excretion rate appeared to have been suppressed in sodium-loaded groups, whether potassium-supplemented or not, but the variance within each group was large, and significant levels of suppression were not reached. Heart rates among these groups, however, were significantly decreased, indicating that systemic adrenergic tone was indeed diminished. In contrast to the likely reduction of the UE excretion rate, the UNEV excretion rate of moderately hypertensive animals returned to a rate comparable to that of the Control Diet group during this period, and the UNEV values of the animals that developed severe hypertension rose to a level that exceeded that of the Control Diet group. If systemic sympathoadrenal activity was decreased among these groups, as indicated by the UE excretion rate and heart rate data, and if a resultant reduction in renal-filtered NE occurred, then an enhanced renal sympathetic tone and renal contribution to UNE in those animals that developed severe hypertension must have occurred such that their UNE values were now greater than that of the Control Diet group. These peak values of UNE excretion in the severely hypertensive groups appeared during their most severe hypertension. Potassium supplementation did not affect this UNEV increase in severely hypertensive animals, but it did moderate the severity and duration of the increased BP. Potassium supplementation did not appear to affect BP in the moderately hypertensive groups. These data indicate that, during the second and third weeks of dietary sodium loading, there was suppressed systemic sympathoadrenal tone at a time of elevated BP that was not affected by dietary potassium supplements. Renal sympathetic tone was likely enhanced among those animals that developed severe hypertension at a time when their hypertension was most severe. A potassium supplement appeared to moderate hypertension only in those animals that developed severe hypertension.

By the end of the 4th dietary week, urinary catecholamine excretion rates of the various groups were indistinguishable from that of the Control Diet group despite the persistence of highly significant differences in BP. Heart rate data were in concurrence with the UNE and UEV data, indicating control levels of sympathetic activity. Only the potassium-supplemented severely hypertensive group maintained a depressed heart rate and, interestingly, their pressures had returned into the moderately hypertensive range at this time. Taken alone, these normal indices of sympathetic adrenergic activity occurring concomitantly with hypertensive levels of BP suggest that adrenergic activity was inappropriately high for the levels of BP observed. The observations that these indices had undergone a transition from an initially depressed state to a control level state during the course of the study, that changes in BP persisted at a constant level in some groups after the first dietary week while indices of sympathetic activity returned to normal, and that potassium supplementation moderated the development of hypertension in severely hypertensive animals despite changes in sympathetic nervous system indices similar to those of nonsupplemented severely hypertensive animals, suggest that there were also changes in responsiveness to adrenergic activity during the dietary periods.
In conclusion, Sprague-Dawley derived rats responded to excess dietary sodium with a rapid increase in BP and depressed indices of sympathoadrenal activity, indicating that the initial increase in BP was not due to sodium-enhanced adrenergic activity. Two subgroups with respect to the susceptibility to sodium-induced hypertension were found within the strain: one that developed moderate hypertension and one that developed more severe hypertension. Animals that developed severe hypertension appear to have excreted more NE at a time when their hypertension was most severe. This enhanced excretion disappeared as their BP fell. The inclusion of a potassium supplement in the high sodium diet appeared to moderate hypertension only in those animals that developed severe hypertension. After 4 dietary weeks, control, moderately hypertensive and more severely hypertensive groups could not be distinguished from one another on the basis of indices of sympathetic nervous system activity. The results of this study taken together with those of earlier observations of blood pressure and catecholamine excretion underscore the importance of studying temporal relationships of factors involved in the genesis of hypertension.

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